Appendix A. Search Strategies Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer

Primary Search Strategy (Ovid MEDLINE)

1. exp Urinary Bladder Neoplasms/
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (cis or Tis or ta or t1$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 1 and 6
8. exp Biological Markers/
9. 7 and 8
10. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. 7 and 10
12. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. exp Surgical Procedures, Operative/
14. exp Drug Therapy/
15. exp Antineoplastic Agents/
16. exp Radiotherapy/
17. (th or su or rt or dh or dt).fs.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18
20. 7 and 19
21. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,

protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. 7 and 21
23. (electromotiv$ or emda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 1 and 23
25. (blue adj5 cystoscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26. 1 and 25
27. exp Radiotherapy/
28. rt.fs.
29. 27 or 28
30. 7 and 29
31. 9 or 11 or 20 or 22 or 24 or 26 or 30
32. exp Urinary Bladder Neoplasms/
33. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
34. (t2$ or t3$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
35. 33 or 34
36. 32 and 35
37. cystectom$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
38. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. 37 or 38
40. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
41. (avoid$ adj7 cystectom$).mp.
42. 40 or 41
43. exp Lymph Node Excision/
44. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
45. 43 or 44

46. (adjuvant$ or neoadjuvant$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
47. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
48. 46 or 47
49. 39 or 42 or 45 or 48
50. 36 and 49
51. 31 or 50
52. limit 51 to yr="1990 -Current"
53. limit 52 to english language
54. limit 52 to abstracts
55. 53 or 54

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. (cis or Tis or ta or t1$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13. Antineoplastic$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. (t2$ or t3$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

37. (adjuvant$ or neoadjuvant$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41
43. limit 42 to yr="1990 -Current"

Database: EBM Reviews – Cochrane Database of Systematic Reviews

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, abstract, full text, keywords, caption text]

Database: EBM Reviews – Database of Abstracts of Reviews of Effects

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, full text, keywords]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, full text, keywords]
3. (cis or Tis or ta or t1$).mp. [mp=title, full text, keywords]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, full text, keywords]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, full text, keywords]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, full text, keywords]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, full text, keywords]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, full text, keywords]

Appendix A. Search Strategies Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer

13. Antineoplastic$.mp. [mp=title, full text, keywords]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, full text, keywords]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, full text, keywords]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, full text, keywords]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, full text, keywords]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, full text, keywords]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, full text, keywords]
27. (t2$ or t3$).mp. [mp=title, full text, keywords]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, full text, keywords]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, full text, keywords]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, full text, keywords]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, full text, keywords]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, full text, keywords]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, full text, keywords]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Database: EBM Reviews – Health Technology Assessment

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]

Appendix A. Search Strategies Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer

Database: EBM Reviews – NHS Economic Evaluation Database

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, text, subject heading word]
3. (cis or Tis or ta or t1$).mp. [mp=title, text, subject heading word]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, text, subject heading word]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, text, subject heading word]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, text, subject heading word]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, text, subject heading word]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, text, subject heading word]
13. Antineoplastic$.mp. [mp=title, text, subject heading word]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, text, subject heading word]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, text, subject heading word]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, text, subject heading word]
21. 1 and 20 (0)
22. (blue adj5 cystoscop$).mp. [mp=title, text, subject heading word]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, text, subject heading word]
27. (t2$ or t3$).mp. [mp=title, text, subject heading word]
28. 26 or 27

29. 25 and 28
30. cystectom$.mp. [mp=title, text, subject heading word]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, text, subject heading word]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, text, subject heading word]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, text, subject heading word]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, text, subject heading word]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, text, subject heading word]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Appendix B. PICOTS

PICOTS	Include
Populations	• Patients with node-negative, non-metastatic muscle-invasive bladder cancer (stages T2, T3, T4a)
Interventions	• Bladder-preserving chemotherapy and/or radiation therapy [KQ 1, KQ 4] • Partial cystectomy [KQ 1; KQ 4] • Maximal TURBT [KQ 1; KQ 4] • Regional lymph node excision in conjunction with cystectomy or partial cystectomy [KQ 2] • Cystectomy plus Neoadjuvant and/or adjuvant chemotherapy [KQ 3; KQ 4] • Include: Chemotherapy Regimens: carboplatin and gemcitabine; cisplatin and gemcitabine; "CMV" (cisplatin, methotrexate, and vinblastine) and "MVAC" (methotrexate, vinblastine, doxorubicin, and cisplatin); trials of other cisplatin-based combination regimens. Exclude: Trials that evaluate chemotherapy with a single agent.
Comparators	• Cystectomy alone [KQ 1; KQ 3; KQ 4] • Cystectomy in combination with chemotherapy [KQ 1; KQ 4] • Bladder-preserving chemotherapy, radiation therapy (external beam or interstitial radiation therapy), partial cystectomy, and/or maximal thransurethral resection of bladder tumor [KQ 2]
Outcomes	• Mortality, disease-specific and all-cause (primary outcome) [KQ 1; KQ 2; KQ 3] • Recurrence of bladder cancer [KQ 1; KQ 2; KQ 3] • Progression or metastasis of bladder cancer [KQ 1; KQ 2; KQ 3] • Quality of life [KQ 1; KQ 2; KQ 3] • Functional status [KQ 1; KQ 2; KQ 3] • Complications or adverse effects related to treatment [KQ 4]
Timing	• Any duration of followup
Setting	• Any settings
Study Design	• RCTs, cohort studies must be comparative • Systematic reviews must evaluate quality of individual studies

CMV, cisplatin, methotrexate, and vinblastine; KQ=key question; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PICOTS=populations, interventions, comparators, outcomes, timing, setting; RCTs, randomized controlled trials; T2, tumor stage 2; T3, tumor stage 3; T4a, tumor stage 4a; TURBT, transurethral resection of bladder tumor.

Appendix C. Included Studies

Azuma H, Inamoto T, Ibuki N, et al. Utility of the novel bladder preservation therapy, BOAI-CDDP-radiation (OMC-regimen), for elderly patients with invasive bladder cancer. International Journal of Oncology. 2011 Jan;38(1):13-24. PMID: 21109921.

Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification biasin cancer observational comparative effectiveness research. Value in Health. 2013 Jun;16(4):610-8. PMID: 23796296.

Bono AV, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. Acta Urologica Italica. 1997;11(1):5-8. PMID: No PMID.

Brossner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? BJU International. 2004 Jan;93(1):64-6. PMID: 14678370.

Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Annals of Oncology. 2012 Mar;23(3):695-700. PMID: 21859900.

Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer. 2008 Nov 1;113(9):2471-7. PMID: 18823036.

Dhar NB, Klein EA, Reuther AM, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. Journal of Urology. 2008 Mar;179(3):873-8; discussion 8. PMID: 18221953.

Fleischmann A, Thalmann GN, Markwalder R, et al. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. Journal of Clinical Oncology. 2005 Apr 1;23(10):2358-65. PMID: 15800327.

Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. Journal of Urology. 1996 Feb;155(2):495-9; discussion 9-500. PMID: 8558644.

Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. [Erratum appears in N Engl J Med. 2003 Nov 6;349(19):1880]. New England Journal of Medicine. 2003 Aug 28;349(9):859-66. PMID: 12944571.

Holmang S, Hedelin H, Anderstrom C, et al. Long-term followup of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. Journal of Urology. 1997 Aug;158(2):389-92. PMID: 9224309.

International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. [Erratum appears in Lancet 1999 Nov 6;354(9190):1650]. Lancet. 1999 Aug 14;354(9178):533-40. PMID: 10470696.

International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. Journal of Clinical Oncology. 2011 Jun 1;29(16):2171-7. PMID: 21502557.

Kalogeras D, Lampri E, Goussia A, et al. Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient? Journal of B.U.ON. 2008 Jul-Sep;13(3):353-8. PMID: 18979549.

Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. Journal of Urology. 2003 Mar;169(3):946-50. PMID: 12576819.

Koppie TM, Vickers AJ, Vora K, et al. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer. 2006 Nov 15;107(10):2368-74. PMID: 17041887.

Kotwal S, Choudhury A, Johnston C, et al. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. International Journal of Radiation Oncology, Biology, Physics. 2008 Feb 1;70(2):456-63. PMID: 17904301.

Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU International. 2000 May;85(7):817-23. PMID: 10792159.

Malmstrom PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. Journal of Urology. 1996 Jun;155(6):1903-6. PMID: 8618283.

Appendix C. Included Studies

Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. Journal of Clinical Oncology. 2001 Oct 15;19(20):4005-13. PMID: 11600601.

Nieuwenhuijzen JA, Pos F, Moonen LMF, et al. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. European Urology. 2005 Aug;48(2):239-45. PMID: 16005375.

Pal SK, Ruel NH, Wilson TG, et al. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. Clinical Genitourinary Cancer. 2012 Dec;10(4):246-50. PMID: 22981208.

Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. Journal of Urology. 1998 Dec;160(6 Pt 1):2015-9; discussion 20. PMID: 9817313.

Rincon Mayans A, Rosell Costa D, Zudaire Bergera JJ, et al. Response and progression-free survival in T2 to T4 bladder tumors treated with trimodality therapy with bladder preservation. Actas Urologicas Espanolas. 2010 Oct;34(9):775-80. PMID: 20843454.

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Appendix D. Excluded Studies

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Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi-Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Bekelman, 2013[1] Retrospective cohort Medium	US Population-based SEER-Medicare data 1995-2005	Multi, population-based data	1995-2005 Stages T2 and T3 urothelial cell carcinoma Medicare FFS only, no HMO	Unstaged, combination Radical cystectomy with EBRT or chemotherapy, use of nonplatinum-based chemotherapy with EBRT, chemotherapy alone, EBRT alone, non concurrent chemoradiation. Also excluded deaths within 3 months of diagnosis	A: TURBT, EBRT, and concurrent platinum-based chemotherapy B: Radical cystectomy with or without lymphadenectomy	NR
Holmang, 1997[2] Retrospective cohort High	Sweden Population-based Swedish cancer registry data 1987-1988	Multi	1987-1988 Stage T2 or greater Included patients diagnosed at autopsy	Metastatic disease at presentation	A: EBRT with 3-field box, 60 Gy or more B: Radical TURBT alone C: Radical cystectomy, some of whom received preoperative radiotherapy, 2 of whom received preoperative chemotherapy, no routine lymphadenectomy	≥ 5 years
Kalogeras, 2008[3] Retrospective cohort High	Greece Single institution 1995-2006	Single	1995-2006 Stage T2N0M0	None noted	A: EBRT with box configuration, 64 Gy, no reported of percent that underwent cystectomy B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy	A: mean 38 months (range 5-125 mos) B: mean 37 months (range 8-89 mos)

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Bekelman, 2013[1] Retrospective cohort Medium	Screened: 54,402 Eligible: 6,486 Enrolled: 1,843 Total Analyzed: 1,843 Per Group Analyzed: A: 417; B: 1,426	Age: A: mean 79.3 ± 6.0 years; B: mean 75.4 ± 6.2 years Sex: A: 300/417 male; B: 892/1426 male Stage: NR Functional Status: NR	Unadjusted 5-year survival, A vs. B, log-rank test p-value: Overall: 27.9% vs. 46.5%, p<0.001 Disease-specific: 52.2% vs. 64.5%, p<0.001 Unadjusted Cox models: HR overall mortality A vs. B 1.54, 95% CI 1.33-1.77 Propensity-score adjusted model with propensity score derived from demographic and hospital characteristics not further specified: HR for overall mortality, A vs. B, 1.26, 95% CI 1.05-1.53 IVA with area cystectomy rate as instrument, HR for overall mortality, A vs. B: 1.06, 95% CI 0.78-1.31
Holmang, 1997[2] Retrospective cohort High	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 148 Per Group Analyzed: A: 42; B: 70; C: 36	Age: NR Sex: NR Stage: 79% vs. 63% vs. 83% T2 or T3, 21% vs. 37% vs. 17% T4a Functional Status: NR	Survival at study endpoint (~ 5 years after diagnosis), A vs. B vs. C, log-rank test p-value: Overall: T2/T3, A: 17/30 deaths within 5 years, B: 38/44 deaths within 5 years, C: 28/33 deaths within 5 years; T4a, A: 6/6 dead from bladder cancer within 5-26 months, B: all dead C: 9/9 dead from bladder cancer
Kalogeras, 2008[3] Retrospective cohort High	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 145 Per Group Analyzed: A: 119; B: 26	Age: A: < 70, 39 pts; > 70, 80 pts B: < 70, 10 pts; > 70. 16 pts Sex: NR Stage: all T2 Functional Status: NR	3-year survival, A vs. B, log-rank test p-value: Overall: 39% vs. 69%, p=0.032 Disease-specific: NR Local recurrences: A vs. B Local "disease control" reported as 42% for A, 88% for B

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Bekelman, 2013[1] Retrospective cohort Medium	Withdrawals due to AE: NR Death during post-operative period: excluded Death within 1st year: NR	Propensity scores and IVA		Compared to other observational studies, rigorous definition of bladder-preserving therapy
Holmang, 1997[2] Retrospective cohort High	2 cystectomy perioperative deaths 3 EBRT peri-procedure deaths	None	Western Sweden Oncology Centre and Medical Society of Goteborg	
Kalogeras, 2008[3] Retrospective cohort High	Withdrawals due to AE: 0 Death during post-operative period: 0 Grade 3 toxicities in A: 8/119 diarrhea, 8/119 leukopenia, 3/119 anemia Postoperative complications in B: 46% (most of which were SSIs)	None	None	No adjustment of case-mix differences between study groups

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi-Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Kotwal, 2008[4] Retrospective cohort High	UK Single institution 1996-2000	Single	1996-2000 (sub analysis on 2002-2005) Stages Tis, T1, T2, T3 or T4a urothelial cell carcinoma, complete clinical information available	None reported. Excluded patients found to undergo cystectomy for benign indications	A: Radical radiotherapy with 50-55 Gy in 20 fractions B: Radical cystectomy, including lymphadenectomy in 52/72 patients	Not reported. Did include 5-year survival estimates
Nieuwenhuijzen 2005[5] Retrospective cohort Medium	Netherlands Single institution 1988-2003	Single	1988-2003 Stages T1high grade and T2 urothelial cell carcinoma < 5 cm	Previous EBRT, size of tumor not described For Group A, multiple tumors	A: EBRT with 30 Gy in 15 fractions followed by brachytherapy through suprapubic cystototomy, combined with partial cystectomy in 24 patients B: Radical cystectomy with lymphadenectomy	Not reported, included 5-year and 10-year survival estimates

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Kotwal, 2008[4] Retrospective cohort High	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 169 Per Group Analyzed: A: 97; B: 72	Age (median): 75 years (range: 42-99) vs. 68 years (range: 37-85 years) Male: 75% vs. 65% Stage: 9% vs. 19% Tis or T1, 38% vs. 31% T2, 49% vs. 43% T3 or T4a, 3% vs. 7% unknown Functional Status: NR	5-year survival, A vs. B, log-rank test p-value: Overall: 34.6% vs. 41.3%, p=0.39 Disease-specific: 56.8% vs. 53.4%, p=0.376 8-year survival, A vs. B, log-rank test p-value: Overall: 17.8% vs. 36.4%, p NR Disease-specific: NR Local recurrences: A vs. B 31/97 vs. 27/72 regional or distant recurrences Need for cystectomy NR, commented on 31 local failures and 9 cystectomy patients
Nieuwenhuijzen 2005[5] Retrospective cohort Medium	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 185 Per Group Analyzed: A: 108; B: 77	Age: A: Median: 63 years, range 31-88; B: Median: 63 years, range 36-84 Sex: A: 89/108 male; B: 62/77 male Stage: A: T1: 17/108, T2: 91/108 B: T1: 28/77, T2: 49/77 Functional Status: NR Discrepancy in reporting of tumor sizes, A vs. B: < 3 cm: A 77/108, B 12/77 3-5 cm: A 26/108, B 11/77 Unknown: A 5/108, B 54/77	5-year survival, A vs. B, log-rank test p-value: Overall: 62% vs. 67%, p=0.67 Disease-specific: 73% vs. 72%, p=0.28 10-year survival, A vs. B, log-rank test p-value: Overall: 50% vs. 58%, p=0.67 (only p recorded likely from log-rank) Disease-specific: 67% vs. 72%, p=0.28 (only p recorded likely from log-rank) Local recurrences: A 23/108 with bladder recurrences MV model: Cox proportional hazards model adjusted for age, T stage, grade, no. of tumors Overall: HR 1.6 (0.7-3.6) favoring group B Disease-specific: HR 2.0 (0.8-5.1) favoring group B

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Kotwal, 2008[4] Retrospective cohort High	Withdrawals due to AE: NR Death during post-operative period: 4 Death within 1st year: 21.6% vs. 34.7%, p NR	Cox proportional hazards methods adjusting for tumor stage, grade, hydronephrosis, age, sex, and treatment	None	
Nieuwenhuijzen 2005[5] Retrospective cohort Medium	Withdrawals due to AE: 0 Death during post-operative period: 0 Death within 1st year: NR	Cox proportional hazards methods Adjusting for T-category (T1 vs. T2), grade of differentiation (G2 vs. G3 vs. Gx), N-stage (N0 vs. Nx), age (linear) and tumor multiplicity (solitary vs. multiple).		

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi-Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Rincon Mayans, 2010[6] Retrospective cohort High	Spain Single institution 1994-2007	Single	1994-2007 Stage T2-4N0M0	None noted	A: EBRT with two regimens: 1997-2003 patients received Taxol®-methotrexate-5-fluorouracil-cisplatin, 45-65 Gy concurrent with 5-fluorouracil-cisplatin, and 2 subsequent cycles of chemotherapy; from 2003-2007, patients received Taxol®-gemcitabine-cisplatin, IMRT 55-65 Gy B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy or other surgical details	A: mean follow-up 51 months, median follow-up 39 months B: mean follow-up 29 months, median follow-up 18 months
Sell, 1991[7] Randomized controlled trial High	Denmark Multicenter 1983-1986	Multi	1983-1986 Stages T2, T3, T4a	Age > 70 years Previous EBRT Other malignancies	A: Radical EBRT with 60 Gray B: Preoperative ERBT with 40 Gay followed by radical cystectomy, including lymphadenectomy in 40/61 patients	Median follow-up 50 months, not further stratified
Solsona, 2009[8] Nonrandomized clinical trial Medium	Spain Multicenter 1980-1990	Multi	1989-2005 MIBC Positive biopsy 3 months after radical TURBT	Lymph node involvement, hydronephrosis, residual tumor after TURBT	A: Bladder-sparing chemotherapy with CMV, MVAC, or GC B: Radical cystectomy with lymphadenectomy	Partially reported, reported 84 months among those with a cR to chemotherapy

Appendix E1. Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Rincon Mayans, 2010[6] Retrospective cohort High	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 188 Per Group Analyzed: A: 43; B: 145	Age: NR Sex: NR Stage: A: T1/T2 20 patients, T3/T4 23 patients B: NR Functional Status: NR	3-year progression-free survival, A vs. B, log-rank test p-value: 69±7% vs. 72±5%, p=0.83 5-year progression-free survival, A vs. B, log-rank test p-value: 61±7% vs. 63±7%. p=0.83 Complete response in A in 31 patients (72%)
Sell, 1991[7] Randomized controlled trial High	Screened: NR Eligible: NR Enrolled: NR Total Analyzed: 183 Per Group Analyzed ITT: A: 95; B: 88 Per Group Analyzed Actual: A: 88; B: 66	Age: A: Mean: 61.3 years, B: Mean: 61.3 years Sex: A: 80 vs. 82% Stage: 37% vs. 42% T2, 63 vs. 58% T3 or T4 Functional Status: NR	Median Survival (months), A vs. B, log-rank test p-value: Overall ITT: 20 vs. 18, Overall Actual: p=0.08 trend favoring Group A Survival of salvage cystx patients did not differ from Group B Local recurrence, A vs. B: 6.8% vs. 35.8% Distant recurrence, A vs. B: 34% vs. 31.5%
Solsona, 2009[8] Nonrandomized clinical trial Medium	Screened: NR Eligible: NR Enrolled: 146 Total Analyzed: 146 Per Group Analyzed: A: 75; B: 71	Age: A: median 62 years; B: median 64 years Sex: A: 68/75 male; B: 62/71 male Stage: NR Functional Status: NR	5-year survival, A vs. B, log-rank test p-value: Disease-specific: 64.5% vs. NR, p=NS but NR Need for cystectomy in 54/75 Group A patients

Appendix E1. Key Question 1: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Rincon Mayans, 2010[6] Retrospective cohort High	Withdrawals due to AE: NR Death during post-operative period: NR Toxicities in A: NR Postoperative complications in B: NR	None	None	No adjustment of case-mix differences between study groups
Sell, 1991[7] Randomized controlled trial High	Withdrawals due to AE: NR Death during post-operative period: 0 Death within 1st year: NR Moderate or greater GI side effects, A vs. B: 19/95 vs. 22/88 Contracted bladder in 9/61 Group A patients		Danish Cancer Society	Antiquated clinical regimen
Solsona, 2009[8] Nonrandomized clinical trial Medium	Withdrawals due to AE: NR Death during post-operative period: NR Death within 1st year: NR Table 5 reports Group A chemo-related toxicity including Grade ≥ 3 leucopenia in 32%, neutropenia in 66%, anemia in 13%, thrombocytopenia in 25%	Cox proportional hazards methods adjusting for age, sex, presence of bladder Tis, antecedents, size, clinical response, and chemotherapy modality		

AE=adverse event; CI=confidence interval; CMV=cisplatin, methotrexate, vinblastine ; cR=clinical response; EBRT=external beam radiation therapy; FFS=fee-for-service; G=gemcitabine plus cisplatin; GI=gastrointestinal; Gy=gray; HMO=Health Maintenance Organization; HR=hazard ratio; IMRT=Intensity Modulated Radiation Therapy; ITT=intention-to-treat analysis; IVA=instrumental variable analysis; M0=metastasis stage 0;MIBC=muscle invasive bladder cancer; MVAC=Methotrexate, Vinblastine, Doxorubicin, Cisplatin; N0=node stage 0; NR=not reported; NS=not significant; Nx=nodes not removed or unknown; RCT=randomized controlled trial; SEER=Surveillance, Epidemiology and End Results; T1=Tumor stage 1; T2=Tumor stage 2; T3=Tumor stage 3; T4=Tumor stage 4; T4a=Tumor stage 4a; Tis=carcinoma in situ; TURBT=transurethral resection of bladder tumor; UK=United Kingdom

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Brossner, 2004[9] Retrospective Cohort High	Austria and Italy Two centers 1998-2002	Patients undergoing radical cystectomy, American Society of Anesthesiologists grade 2 or 3	NR	A: (Italian Cohort): Cystoprostatectomy in men or pelvectomy in women, with "extended" lymphadenectomy, including the perivesical, hypogastric, obturator, external iliac, common iliac and aortal lymph nodes, into the region of the inferior mesenteric artery. B: (Australian cohort): Cystoprostatectomy in men or pelvectomy in women, with "minimal" lymphadenectomy, including perivesical lymph nodes and lymphatic tissue of the obturator fossa, confined laterally by the external iliac vein and medial by the Obturator nerve.

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Brossner, 2004[9] Retrospective Cohort High	30 days Unclear method of follow-up	A: 46 B: 46	Age (mean): 66.3 vs. 68.2 years Male: Not reported Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: pT1: 4 vs. 6; pT2-3a: 24 vs. 18; pT3b-4: 18 vs. 22; Node positive: 18 vs. 10 Grade: Not reported Functional Status: Not reported	Median operative duration (minutes): 330 vs. 227

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Brossner, 2004[9] Retrospective Cohort High	Median ICU stay (days): 4.5 vs. 5.1, P-value NR Median hospital stay (days): 16.3 vs. 14.2, P-value NR Median blood units received during surgery: 0.8 vs. 1.15, P=0.37 Median blood units received within 30 days: 0.7 vs. 3.2, P=0.067 Complications within 30 days: Overall surgical complications: 20/46 vs. 17/46, P=0.08 Perioperative mortality: 4.3% (2/46) (pneumonia) vs. 2.2% (1/46) (pulmonary embolus), RR 0.50 (95% CI 0.047 to 5.32) Complications requiring surgery: 5/46 vs. 4/46, P=0.28 Cardiac arrhythmia: 5/46 vs. 3/46, P=0.16 Pulmonary embolus: 1/46 vs. 2/46 Pneumonia: 2/46 vs. 7/46, P=0.02 Prolonged ileus >6 days: 1/46 vs. 2/46 Hydronephrosis: 3/46 vs. 6/46 Pyelonephritis: 4/46 vs. 4/46 Acute renal failure: 1/46 vs. 0/46 Transient cerebrovascular accident: 3/46 vs. 1/46	NR	

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Dhar, 2008[10] Retrospective Cohort High	USA and Switzerland Two centers 1987-2000	TCC of bladder (preoperative stage N0M0) who underwent curative intent radical cystectomy	Neoadjuvant treatment, positive pathological margins, stages pTa, pT1, and pT4 cancer	A (Switzerland cohort): Cystectomy with extended lymphadenectomy, with cephalad dissection extended to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of internal iliac vessels. A (USA cohort): Cystectomy with limited lymphadenectomy, with boundaries of the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein.

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Dhar, 2008[10] Retrospective Cohort High	5 years A: Every 6 months for 2 years and annually thereafter. B: 3 and 6 months after surgery, 6-month intervals until 5 years and annually thereafter.	A: 322 B: 336	Age (median): 66.9 vs. 61.6 years, p<0.001 Male: 78% vs. 79% Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: NR Tumor grade: NR Functional status: NR	A vs. B <u>Lymph Nodes</u> Number of nodes examined, median (range): 12 (2-31) vs. 22 (10-43) Number of positive nodes, median (range): 1 (1-5) vs. 2 (1-26) Lymph node positive rate: overall, 13% vs. 26%; pT2, 15/200 vs. 24/150; pT3, 29/136 vs. 59/172 <u>5 year recurrence-free survival</u> (median followup: 25 vs. 40, p<0.001) pT2: 71% vs. 63%, p=0.10 pT3: 19% vs. 49%, p<0.0001 <u>5 year overall survival</u> (median followup: 36 vs. 51, p<0.001) pT2: 64% vs. 61%, p=0.10 pT3: 22% vs. 42%, p=0.0002 <u>Progression:</u> local or systemic: 55% (184/336) vs. 40% (130/322) RR 0.74 (95% CI 0.63 to 0.87) Local progression (p for log-rank test):: pT2: 24% vs. 44%, p<0.0001 pT3: 60% vs. 10%, p<0.0001 Systemic progression (includes those with both local and systemic progression): pT2: 14% vs. 27%, p=0.0048 pT3: 20% vs. 45%, p=0.0012

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Dhar, 2008[10] Retrospective Cohort High	NR	NR	N's in table do not correspond to percentages reported in the paper. Percentages are presented here for RFS and OS. Should we do the same for progression? I am unclear as to what denominator was used when calculating p-values.

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Konety, 2003[11] Retrospective cohort Medium	USA Population based study (SEER data) 1988-1996	primary bladder cancer; subset with radical cystectomy with or without lymph node dissection	NR	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 0 (n=645), 1-3 (n=203), 4-6 (n=239), 7-9 (n=164), 10-14 (n=163), 15-19 (n=106), ≥20 (n=81), missing data.
Leissner, 2000[12] Retrospective cohort	Germany 1986-1997	Radical cystectomy with curative intent for pTis, pT1G3, pT2 to pT4 transitional cell carcinoma	previous pelvic lymphadenectomy or irradiation, preoperative chemotherapy for bladder cancer, pTa bladder cancer	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 1-5, 6-10, 11-15, 16-20, and >20

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Konety, 2003[11] Retrospective cohort Medium	Minimum 2 years; Median in surviving post-cystectomy patients: 63.5 months	Cystectomy subset: N=1923 0 lymph nodes, n=645 ≥1 lymph node, n=956 unknown lymph nodes, n=322	Age: <35: 70 (3.6%); 35-44: 86 (4.5%); 45-54: 237 (12.3%); 55-64: 476 (24.8%); 65-74: 681 (35.4%); 75-84: 349 (18.2%); ≥85: 24 (1.3%) Male: 1265/1923 (65.8%) Race: White: 1698/1923 (93.6%); Black: 117/1923 (6.5%) Smoking Status: NR Recurrent bladder cancer: NR Stage: In situ or 1: 150 (12.9%); Stage 2: 249 (21.4%); Stage 3: 300 (25.8%); Stage 4: 465 (39.9%); missing: 759 Tumor grade: NR Functional status: NR	Risk of death by number of lymph nodes examined; Adjusted hazard ratio (95%CI); p-value: 0: 1 (reference) 1-3: 0.93 (0.69 to 1.27); 4-6: 0.52 (0.36 to 0.76); 7-9: 0.57 (0.39 to 0.81); 10-14: 0.38 (0.25 to 0.57); 15-19: 0.57 (0.39 to 0.85); ≥20: 0.48 (0.30 to 0.76); ≥4: 0.53 (0.36 to 0.76)
Leissner, 2000[12] Retrospective cohort	Minimum 2 years; Mean: 38.7 months	Per group: NR, Overall: 302	Age: 62.8 years Male: male: female ratio 4.5:1 Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage of disease (for all patients with radical cystectomy): pTis: 15 (3.4%); pT1: 100 (22.4%); pT2a: 88 (19.7%); pT2b: 51(11.4%); pT3: 146 (32.7%); pT4: 47 (10.5%) Tumor grade: NR Functional status: NR	≥16 nodes removed vs. ≤15 nodes removed : 5-year bladder cancer- specific survival: 65% vs. 51%, p<0.013 Local recurrence: 17% vs. 27%, p<0.01 Distant metastasis: 10.5% vs. 17%, p<0.01

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Konety, 2003[11] Retrospective cohort Medium	NR	NR	
Leissner, 2000[12] Retrospective cohort	Inverse relationship between number of complications associated with the lymphadenectomy and the number of lymph nodes removed, data NR	NR	

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Poulsen, 1998[13] Retrospective cohort High	Denmark Single study 1990-1997	Radical cystectomy with lymphadenectomy	Pretreatment of bladder cancer	A: Radical cystectomy with extended lymphadenectomy, bounded proximally by bifurcation of the aorta, laterally by the genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal ileac vessel, including the presacral nodes and obturator fossa B: Cystectomy with limited lymphadenectomy, bounded proximally by bifurcation of the common iliac vessels, while the lateral, distal and posterior boundaries were the same as for the extended dissection, including dissection of the obturator fossa.
Shirotake, 2010[14] Retrospective cohort Medium	Japan Single center 1987-2008	Refractory non-muscle-invasive or muscle-invasive bladder cancer	Noncurative surgery, tumors of nonurothelial origin, unclear medical history	A: Cystectomy with lymphadenectomy B: Cystectomy without lymphadenectomy Neoadjuvant chemotherapy, n=16, mostly T3-4 Adjuvant chemotherapy, n=26, T3-4 or Node positive

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional	Results
Poulsen, 1998[13] Retrospective cohort High	4-month intervals for the first year, then annually.	A: n=126 B: n=68	Age, mean: 61.8 vs. 63.2 years Male: 102/126 vs. 55/68 Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: T0-Ta: 7.1% vs. 5.9%; Tis: 13.5% vs. 5.9%; T1: 12.7% vs. 25%; T2: 10.3% vs. 13.2%; T3a: 13.5% vs. 16.2%; T3b: 35.7% vs. 29.4%; T4a: 4.0% vs. 1.5%; T4b: 1.6% vs. 1.5%; prostate: 0.8% vs.	A vs. B: Median number of nodes removed: 25 (range 9-67) vs. 13 (range 6-30), p<0.0001 5-year recurrence-free survival: 62% vs. 56%, p=0.33 5-year risk of distant metastasis: 29% vs. 30%, p not reported 5-year risk of pelvic metastasis: 10% vs. 10%, p not reported 5-year recurrence-free survival: Stage ≤T3a: 85% vs. 64%, p<0.02; Stage ≥T3b: 27% vs. 39%, p=0.87 5-year survival: Stage ≤T3a,N0: 90% vs. 71%, p<0.02; Stage ≥T3b,N0: 38% vs. 67%, p=0.46
Shirotake, 2010[14] Retrospective cohort Medium	3-month intervals for 2 years and every 6 months thereafter	A: 107 B: 62 (includes those without lymphadenectomy or unknown number of nodes removed)	Age, mean: 67.65 vs. 69.4 years Male: overall 127/169 Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: ≤T2: 52/107 vs. 34/62; T3-4: 55/107 vs. 28/62 Tumor grade: G1-2: 27/107 vs. 28/62; G3: 80/107 vs. 38/62 Functional status: NR	Node positive (N+) vs. Node negative (N-) vs. Nodes not removed or unknown (Nx) 5-year Cancer-specific survival: 40.8% vs. 72.3% vs. 73.5%; N+ vs. N-, p=0.0471, Nx vs. N-, p=0.846 ≥9 nodes removed vs. <9 nodes removed: 5-year Cancer-specific survival, node-positive and node negative patients: 84.3% vs. 52.7%, adjusted HR 3.48 (95%CI 1.50 to 9.31) Node negative patients: adjusted HR 6.94 (95% CI 1.88 to 38.21)

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Poulsen, 1998[13] Retrospective cohort High	NR	Mauritzen La Fontaine Foundation	
Shirotake, 2010[14] Retrospective cohort Medium	NR	NR, Authors disclosed no COI	

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Simone, 2013[15] Retrospective cohort Medium	Italy Two centers 2002-2010	high-grade urothelial carcinoma	neoadjuvant treatment, salvage cystectomy	A: Cystectomy with extended lymphadenectomy, dissected nodes up to and, in some cases, above the aortic bifurcation including the presacral nodes B: Cystectomy with standard lymphadenectomy, dissected nodes with an upper boundary at the iliac bifurcation (not including presacral and common nodes)

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Simone, 2013[15] Retrospective cohort Medium	followup method, NR	A: 349 B: 584	Age, mean: 65.4 years vs. 66.9 years Male: 309/349 vs. 502/584 Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: T0, a, is, 1: 94/349 vs. 140/584; T2: 98/349 vs. 131/584; T3: 108/349 vs. 235/584; T4: 49/349 vs. 78/584 Tumor grade: NR Functional status: NR	Number of nodes removed, A vs. B, mean (SD): 32.7 (14.9) vs. 16.6 (11.8), p<0.001 Lymph node invasion found: 111/349 vs. 187/584, p=0.56 Bladder cancer specific survival: Adjusted HR 1.80 (95% CI 1.37 to 2.37)

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Simone, 2013[15] Retrospective cohort Medium	NR	NR, Authors disclosed no COI	No details on how patients were selected for the two procedures

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Zehnder, 2011[16] Retrospective cohort High	USA and Switzerland Two centers 1985-2005	Radical cystectomy with lymphadenectomy with curative intent for T2-3, clinically N0M0 bladder cancer	Neoadjuvant treatment, positive soft tissue margins, T1 or T4 bladder cancer	A (USA cohort): Cystectomy with lymphadenectomy, pure intrapelvic template plus removal of lymphatic tissue along the common iliac vessels, the distal vena cava/aorta to the IMA takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa. B (Switzerland cohort): Cystectomy with lymphadenectomy, pure intrapelvic template ended proximally at the mid-upper third of the common iliac vessels, included the presacral region medial to the internal iliac vessels but left tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation Both groups used pure intrapelvic template for lymphadenectomy, with boundaries of the genitofemoral nerve and the pelvic side wall laterally, the circumflex iliac vein and Cloquet's node distally, the obturator fossa with full exposure of the intrapelvic course of the obturator nerve and the internal iliac vessels posteriorly, and the tissue medial to these vessels.

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Zehnder, 2011[16] Retrospective cohort High	A: 4-month intervals in year 1, 6-month intervals in year 2, annually thereafter; Median followup: 10.9 years B: 3, 6, 12 months postoperatively, annually thereafter; Median followup: 9.9 years	A: 554 B: 405	Age, median: 67 vs. 67 years Male: 421/554 vs. 314/405 Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: T2: 253/554 vs. 169/554; T3: 301/554 vs. 236/405 Tumor grade: G3: 534/554 vs. 390/405 Functional status: NR	Pathologically Node-positive: 195/554 vs. 114/405 Recurrence: 38% (210/554) vs. 38% (154/405), RR 1.0 (95% CI 0.85 to 1.17) Recurrence-free survival: ~58% in each group (p=0.75) Overall survival: ~17% in each group (p=0.45)

Appendix E2. Key Question 2: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Zehnder, 2011[16] Retrospective cohort High	NR	NR	

CI = confidence interval; COI = conflict of interest; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; ICU = intensive care unit; IMA = inferior mesenteric artery; M0 = Metastasis stage 0; N = Nodes; N- = Node positive; N+ = Node negative; N0 = Node stage 0; NR = Not reported; Nx = Nodes not removed or unknown; OS = overall survival; PICOTS = populations, interventions, comparators, outcomes, timing, study designs; pT1 = Tumor stage 1 determined by pathology; pT2 = Tumor stage 2 determined by pathology; pT3 = Tumor stage 3 determined by pathology; pT4 = Tumor stage 4 determined by pathology; pTa = Tumor stage a determined by pathology; RFS = recurrence-free survival; SD = standard deviation; SEER = Surveillance, Epidemiology and End Results program; T0 = Tumor stage 0; T1 = Tumor stage 1; T2 = Tumor stage 2; T3 = Tumor stage 3; T3a = Tumor stage 3a; T3b = Tumor stage 3b; T4 = Tumor stage 4; T4a = Tumor stage 4a; T4b = Tumor stage 4b; Ta = Tumor stage a; TCC = transitional cell carcinoma; Tis = carcinoma in situ; USA = United States of America

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Bono, 1997[17] Randomized controlled trial Medium	Italy Nine centers 1984-1987	T2-T4a, and histologically proven muscle-invasive transitional cell carcinoma of bladder, at least 3 cm in diameter without clinical evidence of positive lymph nodes or distant metastases. Creatinine < 1.6 mg/dL, Normal hepatic and respiratory function.	Other histological subtypes of tumor including squamous cell carcinoma; upper tract tumors; other cancers outside of bladder cancer; positive LNs or metastases; "important anemia", uncontrolled diabetes, severe cardiovascular disease, active uncontrolled infections. Early death or surgical complications precluding chemotherapy.	A: Radical cystectomy with LN dissection + adjuvant chemotherapy with cisplatinum 70 mg/m2 day 1, and methotrexate 40 mg/m2 days 8 and 15 every 21 days for 4 cycles starting 21-28 days after surgery (n=35 for pN0 and n= 31 for pN+, total n=66) B: Radical cystectomy with LN dissection (n=48) **pN0 patients were randomized into the groups A or B; pN+ patients were assigned to group A**	Mean: 69.12 months. Method: Every 3 months for 2 years with blood work, chest X-ray, abdominal ultrasound, clinical exam. CT scan of abdomen and bone scan every 6 months for 2 years.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Bono, 1997[17] Randomized controlled trial Medium	Screened: NR Randomized: 125 Post-randomization exclusions: 5 total Lost to follow-up: 2 (excluded from analysis) 4 excluded from analysis for "protocol violation" total 114/125 was analyzed.	Age (mean): 62 vs. 62, 60 in pN+ group Male: 104/114, # in each group NR Race: NR Smoker: NR Recurrent bladder cancer: NR Tumor stage: pT2N0: 20% (7/35) vs. 27% (13/48), pT2N+: 10% (3/31) pT3aN0: 43% (15/35) vs. 39% (18/48), pT3aN+: 32% (10/31) pT3b-4aN0: 37% (13/35) vs. 35% (17/48), pT3b-4aN+: 58% (18/31) Nodal status: pN+ 22% (31/114)	pN0 A vs. B Progression: 51% (18/35) vs. 56% (27/48) No progression: 49% (17/35) vs. 44% (21/48), RR 0.91 95% CI 0.61-1.37 Survival: 49% (17/35) vs. 38% (18/48) Died of disease: 46% (16/35) vs. 52% (25/48), RR 0.88 95% CI 0.56-1.38 Death, any cause: 51% (18/35) vs. 63% (30/48) pN+ from group A Progression: 58% (18/31) No progression: 42% (13/31) Survival: 32% (10/31) Died of disease: 58% (18/31) Death, any cause: 68% (21/31)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Bono, 1997[17] Randomized controlled trial Medium	Chemotherapy toxicity grade 3 or greater: nausea/vomiting: 9/66 mucositis: 13/66 renal toxicity: 11/66 hematologic toxicity (not specified): 1/66 other (not specified): 1/66 Discontinuation of chemotherapy 10.6% (7/66)		chemotherapy discontinued prior to completion of 4 cycles in 4/31 in pN+ group and 3/35 in pN0 group.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Cognetti, 2012[18] Randomized controlled trial Medium	Italy 45 centers 2001-2007	pT2G3 (N0-2), pT3-4(N0-2) any G, pN1-2 any T or G Radical cystectomy with no residual tumor Minimum of 10 LNs dissected Eastern Cooperative Oncology Group performance status 0-2 Age <= 75 "Adequate bone marrow reserve" "good renal (Cr <= 1.25 micromole/L, CrCl >= 60 mL/minute) and liver function"	Prior neoadjuvant chemotherapy or radiotherapy	A: Cystectomy +/- LN dissection + AC every 28 days for 4 cycles with gemcitabine 1000 mg/m2 days 1,8, and 15 plus cisplatin 70 mg/m2 on day 2 or day 15 (GC) (total n=97; cisplatin day 2 (A1), n=43, cisplatin day 15 (A2), n=46) B: Cystectomy +/- LN dissection + treatment on relapse (n=86)	Median: 35 months Method: Every 3 months for 2 years, then every 6 months for 3 years, then yearly thereafter. CT scans every 6 months for 3 years then yearly thereafter.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Cognetti, 2012[18] Randomized controlled trial Medium	Screened: NR Randomized: 194 (102 vs. 92) Post-randomization exclusions: NR Lost: 11 (5 vs. 6) 8/97 patients randomized to arm A (AC) refused initiation of chemotherapy (unsure whether A1 or A2)	Age (mean): 64 vs. 63 Male: 93% (90/97) vs. 87% (75/86) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: pT1: 3% (3/97) vs. 1% (1/86) pT2: 30% (29/97) vs. 22% (19/86) pT3: 47% (46/97) vs. 57% (49/86) pT4: 9% (9/97) vs. 20% (17/86) Grade of tumor: G2: 3% (3/97) vs. 5% (4/86) G3: 93% (90/97) vs. 93% (80/86) Gx or missing: 4% (4/97) vs. 2% (17/86) LN status: pN0: 48% (47/97) vs. 57% (49/86) pN1: 21% (20/97) vs. 22% (19/86) pN2: 31% (30/97) vs. 21% (18/86) Functional status: ECOG PS 0: 81% (79/97) vs. 71% (61/86) ECOG PS 1-2: 17% (16/97) vs. 24% (21/86) ECOG PS missing: 2% (2/97) vs. 5% (4/86) Tumor type: TCC: 98% vs. 99%; other: 2% vs. 1%	A vs. B Overall recurrence: 44% (43/97) vs. 47% (40/86), RR 0.95 95% CI 0.69-1.31 5 year disease-free survival: 42% vs. 37%, p=0.70, HR 1.08, 95% CI 0.73-1.59 5-year disease free survival in node-negative patients: 58% vs. 60%, p=0.97 5 year disease free survival in node-positive patients: 19% vs. 19%, p=0.80 5 year overall survival: 43% vs. 54%, , p=0.24 5 year overall survival A1 vs. A2: 47% vs. 40%, p=0.88 5-year overall survival lymph node negative disease: 65% vs. 73%, p=0.65 5-year overall survival lymph node positive disease: 26% vs. 28% p=0.71 HR for mortality A vs. B: HR = 1.29, CI 0.84-1.99, p=0.24 Independent of treatment arm, mortality hazard was significantly associated with nodal status and T stage: pN1 vs. pN0: HR =2.42, CI 1.38-4.26 pN2 vs. pN0: HR =4.33, CI 2.6-7.2 pT3 vs. pT1-2 HR= 2.01, CI 1.14-3.56 pT4 vs. pT1-2 HR =2.57, CI 1.34-4.92

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cognetti, 2012[18] Randomized controlled trial Medium	Toxic effect AC (all %/ grade 3/4 %) groups A1 vs. A2 Leukopenia: 65%/9% vs. 66%/15% neutropenia: 68%/21% vs. 70%/35% anemia: 63%/5% vs. 55%/6% thrombocytopenia: 49%/26% vs. 45%/4% (p= 0.006 for grade 3/4 A1 vs. A2) Fever: 39% vs. 28% n/v: 48%/9% vs. 54% /2% cephalea 7% vs. 4% diarrhea: 19%/2% vs. 17% stomatitis/mucositis: 21% vs. 11% decrease in Creatinine clearance: 14%/2%vs. 9% proteinuria: 14% vs. 4% alopecia: 28% vs. 23% infection 21%/5% vs. 11%% asthenia: 65%/5% vs. 46%/2% Dose reduction/ early stop of therapy A1 vs. A2: 67%/39% vs. 72%/26%	Italian Minister of Health	Study underpowered Group B: 23/40 relapses received some kind of chemotherapy, 3/40 received surgery or RT, 5/40 supportive care, 9/40 missing data. Group A: 21/43 relapses received other chemotherapy, 5/43 surgery or RT, 11/43 supportive care, 6/43 missing data. Group A: 92% completed first cycle AC, 78% 2 cycles, 74% 3 cycles, 62% all 4 cycles.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Dash, 2008[19] Retrospective cohort High	United States Single Center 2000-2006	Muscle-invasive bladder cancer, T2-T4a, N0; received NAC with Gemcitabine/Cisplatin or MVAC	Clinical indication of metastatic disease, including adenopathy >2cm, non transitional cell carcinoma, T4b disease	A: NAC: Gemcitabine + Cisplatin, predominately given as: "Single dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 70 mg/m2 and gemcitabine 1000 mg/m2 on day 1, and gemcitabine 1000 mg/m2 on day 8. "Split-dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 35 mg/m2 and gemcitabine 1000 mg/m2 on days 1 and 8. B: NAC: Methotrexate, vinblastine, doxorubicin and cisplatin given as 4 cycles at 28-day intervals. Doses were not reported.	Overall duration of followup: NR Median followup for survivors: Gemcitabine/ Cisplatin: 24.2 months; MVAC: 48.1 months Followup method: NR
Freiha,1996[20] Randomized controlled trial Medium	USA Single Center 1986-1993	Stage T3b-4N0/+M0, TCC of bladder who underwent radical cystectomy with LN dissection	NR	A: Radical cystectomy with LN dissection + AC, 4 cycles every 21 day with methotrexate 30 mg/m2, and vinblastine 4 mg/m2 day 1 and 8, 100 mg/m2 cisplatin on day 2 (CMV) (n= 25) B: Radical cystectomy with LN dissection (n=25)	Mean, median: 57 and 62 months Method: Every 3 months for year 1, every 4 months for year 2 and every 6 months thereafter. Physical exam, blood studies, chest X-ray. Urine cytology every 6 months. CT at months 3,6,9,15,24

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Dash, 2008[19] Retrospective cohort High	Screened: A: >700; B: NR Randomized: NA Analyzed: A: 42; B: 54	A vs. B Age (median): 64 vs. 63 Male: 76% (32/42) vs. 8% (43/54) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: T2: 45% (19/42) vs. 59% (32/54) T3: 45% (19/42) vs. 28% (15/54) T4: 10% (4/42) vs. 13% (7/54) Tumor grade: NR Functional status: NR	GC results only. No statistical comparisons of A vs. B. Downstaging tumor at cystectomy: Overall: pT0: 26% (95%CI: 14-42); <pT2: 36% (95%CI: 21-52) <pT2, standard-dose cisplatin: 13/27; <pT2, split-dose cisplatin: 2/15; No statistical comparison, RR 0.60 95% CI 0.40-0.91
Freiha,1996[20] Randomized controlled trial Medium	Screened: 56 Randomized: 50 (27 vs. 28) Post-randomization exclusions: 5 (2 vs. 3) Lost to follow-up: NR	Age (mean): 59 vs. 64 Male: 92% (23/25) vs. 88% (22/25) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: T3bN0: 16% (4/25) vs. 28% (7/25) T4N0: 12% (3/25) vs. 4% (1/25) pN+,1 node: 16% (4/25) vs. 40% (10/25) pN+, 2 nodes: 20% (5/25) vs. 12% (3/25) pN+, 3 nodes: 16% (4/25) vs. 8% (2/25) pN+, 4+ nodes: 20% (5/25) vs. 8% (2/25) Grade: G2: 4% (1/25) vs. 0% (0/25) G3: 12% (3/25) vs. 28% (7/25) G4 84% (21/25) vs. 72% (18/25) Functional status: NR	A vs. B Recurrence: 52% (13/25) vs. 76% (19/25), RR 0.68 95% CI 0.44-1.06 with mean / median interval to recurrence: 17.5 /16.2 months (4-37 months) vs. 11.5 / 10.1 months (2-34 months), p=0.01, log rank test **6/19 recurrences in group B, 6 received CMV therapy** Survival: 52% (13/25) vs. 32% (8/25), p=0.32, log rank test, RR 0.71 95% CI 0.42-1.15 Mean and median survival time 56 and 63 months vs. 42 and 36 months Survival according to nodal status N0: 71 % (5/7) vs. 25% (2/8), RR 0.38 95% CI 0.11-1.31 N+: 44% (8/18) vs. 35% (6/17) <= N3: 46% (6/13) vs. 40% (6/15) > N3: 40% (2/5) vs. 0% (0/2)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Dash, 2008[19] Retrospective cohort High	Hospitalized during treatment: 9/42	NR	Retrospective cohort, does not report comparisons between MVAC and GC
Freiha,1996[20] Randomized controlled trial Medium	1/25 death from neutropenia and sepsis after cycle 1 of CMV 2/50 deaths from MI after cystectomy (at 40 days and 72 months - not sure from which group) 2/25 in group A episodes of neutropenia and fever requiring hospitalization 8/25 Group A neutropenia that delayed chemotherapy 1/50 Group A heart failure that recovered (? group) 3/25 Group A decrease in GFR requiring modification to chem dosing (2 of 3 recovered fully, 1 had creatinine of 2.6 after last cycle of chemotherapy) 8/25 Group A GI toxicity (2 bleeding, 2 mucositis, 4 nausea and vomiting) 2/25 Group DVT (1 leading to nonfatal PE) (? group)	NR	Patients randomized to observation (group B) who showed evidence of recurrence were treated with CMV chemotherapy. One patient received 5-fluorouracil with CMV

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Grossman, 2003[21] Randomized controlled trial Medium	USA 126 centers 1987-1998	T2-4aN0M0 who were candidates for radical cystectomy, "adequate renal, hepatic, and hematologic function", SWOG performance status 0-1	Prior pelvic irradiation	A: neoadjuvant chemotherapy (NAC), three 28-day cycles with methotrexate 30 mg/m2 on days 1, 15 and 22; vinblastine 3 mg/m2 on days 2, 15 and 22; doxorubicin 30 mg/m2 and cisplatin 70 mg/m2 on day 2 (M-VAC) + cystectomy with LN dissection (n=153) B: Cystectomy with LN dissection (n=154)	Median: 8.7 years vs. 8.4 years

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Grossman, 2003[21] Randomized controlled trial Medium	Screened: NR Randomized: 317 (158 vs. 159) Post-randomization exclusions: 10 (5 vs. 5) Lost to follow-up: NR	Age (mean): 63 vs. 63 Male: 83% (127/153) vs. 81% (124/154) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: T2: 40% (61/153) vs. 40% (61/154) T3/T4a: 60% (92/153) vs. 60% (93/154) Functional status: NR	A vs. B Downstaging tumor (pT0 at time of surgery): 38% (48/126) vs. 12% (15/121), p=<0.001 Deaths: 59% (90/153) vs. 65% (100/154) over follow-up period with Median survival (months), unstratified: 77 vs. 46, p=0.05 log rank test Survival at 5 years 57% vs. 43%, p=0.06 Median survival (months) stratified for age: age <65: 104 vs. 67, age >= 65: 61 vs. 30 p=0.05, log rank test Median survival (months) stratified for tumor stage: T2: 105 vs. 75; T3/T4a: 65 vs. 24, p=0.05, log rank test Cystectomy only group had a 33% increased risk of death compared to the M-VAC/cystectomy group (stratified analysis) Overall mortality 59% vs. 65%, HR 0.75, 95% CI 0.57 to 1.00 Disease-specific mortality 35% vs. 50%, HR 0.60, 95% CI 0.41 to 0.82, p=0.002

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Grossman, 2003[21] Randomized controlled trial Medium	Group A: 35/150 and 50/150 had grade 3 and 4 granulocytopenia, respectively. 7/150, grade 3 thrombocytopenia. 9/150 grade 3 anemia 30/150 grade 3 GI toxicity (nausea, vomiting, diarrhea, constipation, stomatitis)	Cooperative Agreements with the National Cancer Institute, Dept of HHS.	Planned cystectomy in 82% (27/153) group A, 81% (30/154) group B. 9 patients (2 vs. 7) had cystectomy outside the study. 3/153 decline chemotherapy in group A. 87% of group A received at least one full cycle of M-VAC.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
International Collaboration of Trialists, 1999[22] Randomized controlled trial Medium	20 countries 106 centers 1989-1995	T2G3--T4a TCC of bladder or mixed cell types TCC / squamous or glandular metaplasia. Histologic confirmation of muscle invasion. WBC > 3.5 x10^9, platelets > 100x10^9	Tumors > 7cm by imaging or bimanual palpation, nodal metastases, GFR < 60 mL/minute for first 448 patients, changed to GFR < 50 mL/minute thereafter Prior systemic chemotherapy or radiation. Any other prior cancer	A: NAC every 21 days for 3 cycles with methotrexate 30 mg/m2, vinblastine 4 mg/m2 on day 1 and day 8; cisplatin 100 mg/m2 on day 2 (CMV) + cystectomy +/- LN dissection or radiotherapy (RT) or RT and cystectomy (n=491) B: cystectomy with LN dissection or radiotherapy or RT and cystectomy. (n=485) **Cystectomy as salvage therapy for recurrence in RT group. **local radical treatment chosen before randomization for each patient **radiotherapy protocol permitted a range of radiation dose-schedules. RT prior to cystectomy was 4 Gy x 5days.	Median: 4 years. Method: Option for group A: cystoscopy, bimanual palpation, TURB after 3 cycles of chemotherapy before radiotherapy or cystectomy to assess for response.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
International Collaboration of Trialists, 1999[22] Randomized controlled trial Medium	Screened: NR Randomized: 976 (491 vs. 485) Post-randomization exclusions: NR Lost to follow-up: 6 (4 vs. 2)	Age (median): 64 vs. 64 Male: 433/491 (88%) vs. 430/485 (89%) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: T2: 34% (169/491) vs. 34% (165/485) T3: 58% (285/491) vs. 58% (282/485) T4: 85 (37/491) vs. 8% (38/485) Tumor grade: G1: 1% (6/491) vs. 0.2% (2/485) G2: 11% (52/491) vs. 13% (61/485) G3: 885 (433/491) vs. 87% (421/485) unknown grade: 0% vs. 0.2% (1/485) Functional status: WHO 0: 69% (340/491) vs. 69% (337/485) WHO 1: 26% (130/491) vs. 26% (128/485) WHO 2: 4% (20/491) vs. 4% (19/485) WHO 3: 0.2% (1/491) vs. 0.2% (1/485) Nodal status: N0: 67% (327/491) vs. 63% (307/485) NX: 33% (164/491) vs. 37% (178/485) Radical treatment: Radiotherapy: 42% (207/491) vs. 43% (208/485) Cystectomy: 50% (246/401) vs. 49% (239/485) Radiotherapy + cystectomy: 8% (38/491) vs. 8% (38/485)	A vs. B Locoregional disease free survival: 47% vs. 42%, HR 0.87 (0.73-1.02, p=0.087, Mantel-Cox (M-C) log rank test) Median locoregional disease free survival (months): 23.5 vs. 20 No evidence of a difference between treatments for locoregional control, HR 0.97 (0.79-1.19, p=0.738 M-C log rank) Metastasis free survival: 45% vs. 53%, HR 0.79 (0.66-0.93, p=0.007, M-C log rank test) Median metastasis free survival (months): 32 vs. 25 Disease free survival: 46% vs. 39%, HR 0.82 (0.70-0.97, p=0.019, M-C log rank test) Median disease free survival (months): 20 vs. 16.5 Deaths: 229/491 vs. 256/485 Survival: HR 0.85 (95% CI 0.71-1.02, p=0.075, M-C log rank test) Median survival (months): 44 vs. 37.5 Overall 3 year survival: 55.5% vs. 50% (95% CI for difference -0.5-11.0) no significant interaction with age (p=0.38), sex (p=0.39), WHO performance status (p=0.94). Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR no significant interaction with age (p=0.38), sex (p=0.39), WHO performance status (p=0.94). Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR **No restriction of salvage therapy which was given to 36% (347/976). 11% (37/347) received CMV, 15% (51/347) received other chemotherapy, total 25%, 88/347 received additional chemotherapy (21 vs. 67). 20% (68/347) received radiotherapy, 18% (61/347) had salvage cystectomy; 37 % (130/347) patients underwent other procedures including intravesical chemotherapy.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
International Collaboration of Trialists, 1999[22] Randomized controlled trial Medium	5/491 group A died of toxic effects of chemotherapy (mortality 1%) WHO grade 3-4: leukopenia 16% thrombocytopenia 6.5% neutropenic fever 10% 4 patients did not received planned cystectomy due to chemotherapy toxic effects 18 (6 vs. 12) deaths were attributable to cystectomy (mortality 3.7%) 10.5% post-op wound infections (20 vs. 31)	NR	99/491 in group A did not receive all 3 cycles of chemotherapy; 28/99 received no chemotherapy. 76/561 patients did not receive planned cystectomy; 95/415 (23%) did not receive full planned radiotherapy treatment. 159 (32.4%) underwent cystoscopy after chemotherapy; complete response confirmed in 71/159 (44.7%).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
International Collaboration of Trialists, 2011[23] Randomized controlled trial Medium	20 countries 106 centers 1989-1995	Histologically proven muscle-invasive urothelial cell carcinoma T2-T4a, GFR > 50 mL/minute/1.73 m2	NR	A: NAC every 21 days for 3 cycles methotrexate 30 mg/m2 and vinblastine 4 mg/ m2 on day 1 and 8, cisplatin 100 mg/m2 day 2 (CMV) + radiation therapy (RT), cystectomy or RT and cystectomy (n=491) B: Radiation therapy (RT), cystectomy or RT and cystectomy (n=485) The choice of definitive treatments was based on patient and physician choice, not randomly assigned.	Median: 8 years

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
International Collaboration of Trialists, 2011[23] Randomized controlled trial Medium	Screened: NR Randomized: 976 (491 vs. 485) Post-randomization exclusions: NR Lost to follow-up: 6 (4 vs. 2)	No per group numbers listed Age (mean): 64 Male: 863 (88%) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage: T2: 334 (34%) T3: 567 (58%) T4a: 75 (8%) Functional Status: WHO 0-3 (most 0-1) Local definitive treatment: RT: 415/976, 43% (193 vs. 210) Cystectomy: 485/976, 50% (216 vs. 212) RT + cystectomy: 76/976 (8%)	A vs. B (cystectomy patients only) Locoregional recurrence: 40% (84/212) vs. 39% (84/216) Locoregional disease-free survival 55% (119/216) vs. 65% (137/212), HR 0.74 (95% CI 0.58-0.95, p=0.019) Overall survival in patients: HR 0.74 (CI 0.57-0.96) p=0.022 no interaction related to stage of disease (p=0.35) or nodal status (p=0.96). G3 cancers were associated with greater benefit than G1/G2 cancers (p=0.003 for interaction). Interaction for tumor size close to but did not reach statistical significance (p=0.06)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
International Collaboration of Trialists, 2011[23] Randomized controlled trial Medium	5/491 patients who received CMV died from toxic effects during treatment (mortality rate, 1%) In CMV group WHO grade 3-4 leukopenia, thrombocytopenia and neutropenic fever occurred in 16%, 6.5%, and 10% of patients respectively No grade 3 or 4 renal toxic events occurred, but 26% of those in CMV arm required dose decreases or dose delays because impaired renal function	NR	**The choice of definitive treatment was based on patient and physician choice, NOT randomly assigned**

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Malmstrom, 1996[24] Randomized controlled trial Medium Rintala, 1993[25]	Finland, Norway, Sweden 36 centers 1985-1989	T1g3-T4aNXM0 bladder cancer	Prior radiation therapy or systemic chemotherapy. Prior or current other malignancy	A: NAC, 2 cycles separated by 3 weeks with cisplatin 70 mg/m2 and doxorubicin 30 mg/m2 + RT + cystectomy with LN dissection (n=151) B: RT and cystectomy with LN dissection (n=160)	Malmstrom: Minimum of 5 years Rintala 1993: Mean 18 months for all (1-74) and 47 months for those still alive (21-75). 4 month intervals x 2 years, then every 6 months x 1 year, then yearly (no mention of what was done at follow-up).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Malmstrom, 1996[24] Randomized controlled trial Medium Rintala, 1993[25]	Screened: NR Randomized: 325 (157 vs. 168) Post-randomization exclusions: 14 (6 vs. 8) Lost to follow-up: 2 total	Age (mean): NR Male: 82% (124/151) vs. 76% (122/160) Race: NR Smoker: NR Recurrent bladder cancer: NR Stage of disease: T1g3: 18% (27/151) vs. 19% (31/160) T2: 34% (52/151) vs. 40% (64/160) T3: 46% (69/151) vs. 34% (55/160) T4a: 2% (3/151) vs. 6% (10/160) Functional status: WHO 0: 74% (111/151) vs. 76%(121/160) WHO 1-2: 26% (40/151) vs. 24% (39/160)	Malmstrom: A vs. B Recurrence in those patients with no signs of cancer after cystectomy: total 71/249 (31 vs. 40, RR0.82 (95% CI 0.54-1.24) with median interval to relapse 23 months vs. 14 months, p=0.42) Overall survival at 5 years: 59% vs. 51%, p=0.10, log rank test Cancer specific survival at 5 years: 64% vs. 54%, p=0.07, log rank test Overall survival at 5 years for 266 patients undergoing cystectomy/ resection: 65% vs. 58%, no p value given Cancer specific survival at 5 years for 266 patients undergoing cystectomy/ resection: 71% vs. 62%, no p-value given Relative risk of death, adjusted for tumor stage: RR= 0.69 (95% CI 0.49-0.98) 5 year survival by age Patients < 60 years (N=75): 61% vs. 49%, p=0.21 Patients ≥ 60 years (N=236): 58% vs. 51%, p=0.21 Cancer specific survival at 5 years by tumor grade: T1: 77% vs. 71%, not statistically significant T2 58% vs. 55%, not statistically significant T3-T4a: 52% (n=72) v s. 37% (n=65), p=0.03, log rank test Rintala: Survival, patients with T2-T4a, according to downstaging, p0-1 vs. p2 (n=213), no specific number given but in favor of p0-1, p=0.0005 Downstaging of tumors at time of surgery pT1g3 tumors pre-treatment --> pT0, pTis, pT1: 20/27 vs. 22/31 (p= 0.002, chi-squared test)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Malmstrom, 1996[24] Randomized controlled trial Medium Rintala, 1993[25]	6 deaths (2 vs. 4) within 1 month after cystectomy 16 wound dehiscence (6 vs. 10) 17 small bowel obstruction (13 vs. 4) 8 pelvic abscess (4 vs. 4) 7 thromboembolic events (3 vs. 4) 6 with sepsis (3 vs. 3) 10 urine leakages (6 vs. 4) 32 "other" (not specified) (13 vs. 19)	NR	11% T2-T4a tumors with no histologic proof of muscle invasion; Deviations from scheduled surgery: 21 vs. 26 (2 partial bladder resection, 30 laparotomy only, 15 no laparotomy). No chemotherapy in 10, only 1 cycle in 8 and > 25% reduction cisplatin in 4 and no radiotherapy 8.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Sherif, 2002[26] Randomized controlled trial Medium	Sweden, Finland, Norway Multi-center, number not reported 1991-1997	T2-4aNXM0 urothelial bladder cancer, "normal - moderately reduced kidney function" (by pre-defined nomogram), "acceptable bone marrow function" (WBC > 3 x 10^9/l, platelet >= 100 x 10 ^9/l and WHO performance status <= 2	SCC or adenocarcinoma of bladder, previous RT or chemotherapy, previous history of/or concomitant other malignancy (except in situ cancer cervix or BCC skin)	A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m2, methotrexate 250 mg/m2 + cystectomy with LN dissection (n=155) B: Cystectomy with LN dissection (n=154)	Median: 5.3 years. Method: Every 4 months for 2 years, then every 6 months for 2 years, then yearly for 1 year. (physical exam, creatinine, chest X-ray, Intravenous pyelography at 4, 16 and 36 months).
Skinner, 1991[27] Randomized controlled trial Medium	USA Single center 1980-1988	Surgically confirmed invasive carcinoma of the bladder (TCC or TCC associated with squamous or glandular differentiation with or without carcinoma in situ), stage p3, p4, or N+ and M0, no involved LNs above the aortic bifurcation, age 9-75 years	Prior noncutaneous malignancy within 10 years, prior chemotherapy or pelvic RT, bilirubin > 1.5, serum glutamic oxaloacetic transaminase more than 2 times normal, elevated alkaline phosphatase, WBC < 3.5, platelets < 150,000, Serum Creatinine > 1.0, Karnofsky performance status less than 50, medical/social/ psychological factors that would make patient poor risk for completion of chemotherapy.	A: Cystectomy with LN dissection + AC, 4 cycles at 28-day intervals starting 6 weeks after surgery with cisplatin 100 mg/m2, doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 (n=44) B: Cystectomy with LN dissection (n=47)	Median: 32 months, with all but 6 patients followed beyond 1 year. Method: Every 4 months for 1 year, then every 6 months for 3 years, then yearly thereafter. (Chest X-ray, urogram, laboratory tests, physical exam. CT, MRI or bone scans based on symptoms/ abnormal lab values).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Sherif, 2002[26] Randomized controlled trial Medium	Screened: NR Randomized: 317 (158 vs. 159) Post-randomization exclusions: 8 (3 vs. 5) Lost to follow-up: NR	Age (mean): 64.6 vs. 65.1 Male: 75% (116/155) vs. 86% (133/154) Race: NR Smoker: NR Recurrent bladder cancer: NR Tumor stage: T2: 41% (64/155) vs. 42% (65/154) T3: 52% (80/155) vs. 49% (76/154) T4a: 7% (10/155) vs. 8% (13/154) Tx: 1% (1/155) vs. 0% Functional status: NR	A vs. B Recurrence locoregional and distant mets: 6% (9/155) vs.8% (12/154) Recurrence locoregional only: 10% (15/155) vs. 9% (14/154), RR 1.06, 95% CI 0.53-2.13 Recurrence distant mets only: 13% (20/155) vs. 16% (24/154) None of recurrence statistically significant Overall 5-year survival: 53% vs. 46% (p=0.2375, log rank test) Overall survival HR, HR= 0.8 (0.6-1.1) 5 year survival in T2 group, p=0.5356, log rank test Overall survival HR T2 group, HR = 0.8 (0.5-1.5) 5 year survival in T3-T4a group, p=0.2740, log rank test Overall survival HR T3-T4a group, HR =0.8 (0.6-1.2) Downstaging tumors (defined as pT0 disease compared to other pT-stages): 26.4% (37/140) vs. 11.5% (16/139)
Skinner, 1991[27] Randomized controlled trial Medium	Screened: 498 Eligible: 160 (59 declined) Consented: 101 (10 had pure SCC or adenocarcinoma) Randomized: 91 Post-randomization exclusions: NR Lost to follow-up: NR	Age (median): 61 vs. 62 Male: 77% (34/44) vs. 74% (35/47) Race: NR Smoker: NR Recurrent bladder cancer (prior bladder resections): 7% vs. 19% Tumor stage: T1 or 2: 7% (3/44) vs. 11% (5/47) T3a: 23% (10/44) vs. 15% (7/47) T3b: 45% (20/44) vs. 51% (24/47) T4: 25% (11/44) vs. 23% (11/47) Tumor grade: G2 5% (2/44) vs. 9% (4/47) G3 50% (22/44) vs. 50% (23/47) G4 45% (20/44) vs. 41% (19/47) missing: 0/44 vs. 1/47 Lymph node status: 0 nodes 61% (27/44) vs. 66% (31/47) 1 +LN 16% (7/44) vs. 21% (10/47) 2+ +LN 23% (10/44) vs. 13% (6/47) Functional status: NR	A vs. B Probability of disease recurrence at 3 years: 0.30 (SE=0.08) vs. 0.54 (SE=0.08), p=0.011, unstratified Wilcoxon test Time to recurrence for node negative patients only is significant with p=0.043 Probability of dying from bladder cancer within 3 years: 0.29 (SE=0.08) vs. 0.50 (SE=0.08) Probability of dying of any cause within 3 years: 0.34 (SE=0.08) vs. 0.50 (SE=0.08) No survival benefit of chemotherapy for all patients, p=0.099 For node negative patients only there was not overall survival benefit to chemotherapy, p=0.14 Chemotherapy benefit seen for LN negative and 1 LN positive cases protection from recurrence and the survival advantage were seen in first 3 years, less evident by 5 years. Benefit of chemotherapy was significant for time to recurrence, (p=0.0010, stratified Wilcoxon) and for survival, (p=0.0062 stratified Wilcoxon) after stratifying for the 3 nodal groups N0. N1, N2+)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Sherif, 2002[26] Randomized controlled trial Medium	NR	Swedish Cancer Society, Swedish Society of Medicine, Johanna Hagstrands and Sigfrid Linners Foundation, Finnish Cancer Society	Deviations from protocol: In experimental arm, A, 14 patients received no NAC, 9 received 1 cycle, 14 received 2 cycles and 3 with missing data. In control arm, B, 1 patient received 3 cycles of chemo. 132/155 vs. 139/154 underwent cystectomy
Skinner, 1991[27] Randomized controlled trial Medium	10 total admissions for chemotherapy complications in 7 patients. Cause of hospitalization: neutropenic fever in 5, dehydration in 1, dehydration + neutropenic fever in 4 No chemotherapy related drug toxicity deaths or long term sequelae.	NR	17 patients in group A received individualized chemotherapy regimens, thereafter all received the same regimen. 11/44 patients in group A did not receive chemotherapy; of 33 patients who did receive chemo 1/33 received 6 cycles, 20/33 4 cycles, 2/33 3 cycles, 6/33 2 cycles, 4/33 1 cycle; 32/33 received cisplatin and 25/33 received either doxorubicin or cyclophosphamide.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Wosnitzer, 2012[28] Retrospective Cohort Medium	United States Single Center 1988-2009	T2-T4a, N0-N2, M0	Metastatic disease at initiation of induction or salvage chemotherapy	A: Neoadjuvant chemotherapy, cisplatin or carboplatin based B: Adjuvant chemotherapy, cisplatin or carboplatin based Dosing/Duration: NR	Median followup: A vs. B: 12.8 vs. 14 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Wosnitzer, 2012[28] Retrospective Cohort Medium	Screened: 687 Randomized: NA Post-randomization exclusions: NA Lost to followup: NR Analyzed: 146; A: 73, B: 73	A vs. B: Age (mean): 64 vs. 66 years Male: 52/73 (71%) vs. 53/73 (73%) Race: Caucasian: 60/73 (82%) vs. 56/73 (77%); African American: 3/73 (4%) vs. 2/73 (3%); Latin: 8/73 (11%) vs. 1/73 (1%); Other: 6/73 (8%) vs. 10/73 (14%) Smoker: 20/73 (27%) vs. 19/73 (26%) Recurrent disease: NR Stage of disease >T2: 18/73 (25%) vs. 40/73 (55%); Node status >N0: 5/73 (7%) vs. 29/73 (40%) Tumor grade: NR Functional status: NR	A vs. B Disease specific survival: Univariate HR=1.28 (95%CI: 0.76-2.16), p=0.36; multivariate HR=1.24 (95%CI: 0.70-2.18), p=0.46 Overall survival: Univariate HR=1.12 (95% CI: 0.73-1.73), p=0.60; multivariate HR=1.08 (95% CI: 0.67-1.73), p=0.76 Cisplatin based treatment: median survival: 11 vs. 12.5 months Disease specific survival: NSD, data NR Overall survival: NSD, data NR MVAC treatment: median survival: 16 vs. 22 months Disease specific survival: NSD, p=0.555 Overall survival: NSD, p=0.573 Gemcitabine/cisplatin treatment: median survival: 11 vs. 10.5 months Disease specific survival: HR=10.06 (95%CI: 1.01-112.2), p=0.049 Overall survival: NSD, p=0.607 Carboplatin based treatments: median survival: 8.9 vs. 10 months Disease specific survival: NSD, p=0.764 Overall survival: NSD, p=0.388

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Wosnitzer, 2012[28] Retrospective Cohort Medium	NR	NR	Stage of disease reported as clinical stage in group A, but pathologic stage in group B.

AC=adjuvant chemotherapy; ANC=Absolute neutrophil count; BCC=basal cell cancer; CI=confidence interval; CMV=cisplatin, methotrexate, vinblastine ; Cr=serum creatinine level ; CT=computerized tomography; DVT=Deep venous thrombosis; ECOG =Eastern Cooperative Oncology Group; G=Grade; G1=Grade 1; G2=Grade 2; G3=Grade 3; G4=Grade 4; GC=Gemcitabine plus cisplatin; GFR=glomerular filtration rate; GI=Gastrointestinal; Gy=Gray; HHS=Health and Human Services; HR=Hazard ratio; LN =Lymph Node; M0=without evidence of metastasis; M2=Metastasis stage 2; M-C=Mantel-Cox; MI=Myocardial infarction; MRI=Magnetic resonance imaging; MVAC=Methotrexate, Vinblastine, Doxorubicin, Cisplatin; N+=without regional lymph node involvement; N0=without regional lymph node involvement; N1=Node stage 1; N2=Node stage 2; N3=Node stage 3; NA=Not applicable; NAC=neoadjuvant cisplatin based; NR=Not reported; NSD=no significant difference; Nx=Nodes not removed or unknown; p3=pathological stage 3; p4=pathological stage 4; PE=Pulmonary embolus; PICOTS=Populations, interventions, comparators, outcomes, timing, study designs; pN+=pathologically node-positive; pN0=Node stage 0 determined by pathology; pN1=Node stage 1 determined by pathology; pN2=Node stage 2 determined by pathology; PS=performance status; pT2=Tumor stage 2 determined by pathology; pT3=Tumor stage 3 determined by pathology; pTO=(complete remission) at time of cystectomy; RCT=Randomized Controlled Trial; RR=Relative risk; RT=radiotherapy; SCC=squamous cell carcinoma; SE=standard error; SWOG=Southwest Oncology Group; T=Tumor; T1=Tumor stage 1; T2=Tumor stage 2; T3=Tumor stage 3; T3a=Tumor stage 3a; T3b=Tumor stage 3b; T4=Tumor stage 4; T4a=Tumor stage 4a; T4b=Tumor stage 4b; TCC=Transitional cell carcinoma; TUR=Trans-urethral resection; WBC=white blood cells; WHO=World Health Organization

Appendix F1. Key Question 1: Randomized Controlled Trials Risk of Bias

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?
Sell, 1991[7]	Yes	No	No	Yes	No	No	No

Appendix F1. Key Question 1: Randomized Controlled Trials Risk of Bias

Author, Year	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to-Treat Analysis?	Postrandomization Exclusions	Outcomes Prespecified?	Risk of Bias	Comments
Sell, 1991[7]	Yes	Unclear	Yes	Yes (11 patients in EBRT switched to cystx)	Yes	High	Antiquated treatment regimens not used in contemporary practice

ITT = intention-to-treat; EBRT = external beam radiation therapy

Appendix F2. Key Question 1: Cohort Studies Risk of Bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Bekelman, 2013[1]	Yes	No (but similar in propensity adjusted analysis)	Unclear	Yes	Unclear	Yes (censoring)	Yes	Unclear	Yes	Medium
Holmang, 1997[2]	Yes	Unclear	Unclear	Yes	Unclear	No	No	Unclear	Yes	High
Kalogeras, 2008[3]	Unclear	No	Unclear	Unclear	Unclear	Yes (censoring)	No	Unclear	Yes	High
Kotwal, 2008[4]	Unclear	No	Unclear	No	NR	Yes (censoring)	Unclear (reported in text)	Yes, Yes	Yes	High
Nieuwenhuijzen, 2005[5]	Unclear	No	Unclear	Unclear	Unclear	Yes (censoring)	Yes	Unclear	Yes	Medium
Rincon Mayans, 2010[6]	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Yes	High
Solsona, 2009[8]	Unclear	Yes	Unclear	Yes	Unclear	Yes	No	Unclear	Yes	High

Appendix F3. Key Question 2: Cohort Studies Risk of Bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Brossner, 2004[9]	Yes	Yes	Unclear	Unclear	Unclear	No	No	Unclear	Unclear	High
Dhar, 2008[10]	Unclear	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Yes	High
Konety, 2003[11]	Yes	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Medium
Leissner, 2000[12]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	High
Poulsen, 1998[13]	Yes	Unclear	Unclear	Yes	Unclear	No	No	Unclear	Unclear	High
Shirotake, 2010[14]	Yes	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Medium
Simone, 2013[15]	Unclear	Yes	Unclear	Unclear	Unclear	No	Yes	Unclear	Yes	Medium
Zehnder, 2011[16]	Yes	Yes	Unclear	Unclear	Unclear	No	No	Unclear	Yes	High

Appendix F4. Key Question 3: Randomized Controlled Trials Risk of Bias

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Bono, 1997[17]	Unclear	No	Age: Yes Sex: NR per group Smoking status: NR Bladder cancer stage: Yes	Yes	NR	NR
Cognetti, 2012[18]	Yes	No	Age: Yes Sex: No (male 92% vs. 87%) smoking status: NR Bladder cancer: Yes except pT2 30% vs. 22% and pN2 31% vs. 21%	Yes	NR	NR
Freiha, 1996[20]	Unclear	No	Age: No (59 vs. 64) Sex: Yes smoking status: NR Bladder cancer stage: No	Yes	NR	NR
Grossman, 2003[21]	Yes	No	Age: Yes Sex: Yes Smoking status: NR Bladder cancer stage: Yes	Yes	NR	NR
International Collaboration of Trialists, 1999[22]	Unclear	No	Age: Yes Sex: Yes Smoking status: NR Bladder cancer stage: Yes	Yes	NR	NR

Appendix F4. Key Question 3: Randomized Controlled Trials Risk of Bias

Author, Year	Patient Masked?	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to-Treat Analysis?	Postrandomization Exclusions?	Outcomes Prespecified?	Risk of Bias
Bono, 1997[17]	No	No	Overall: yes (2/125 but not analyzed) Differential: NR	Unclear	Unclear	Unclear	Medium
Cognetti, 2012[18]	No	No	Overall: Yes,11/194 (5.6%) Differential: Yes 5/97 (5.2%) vs. 6/86 (7%)	Yes	Unclear	Yes	Medium
Freiha, 1996[20]	No	No	Unclear	Unclear	Yes total (5/55 = 9%)	Yes	Medium
Grossman, 2003[21]	No	No	Unclear Unclear	Yes	No (total 10/317, 5 vs. 5)	Yes	Medium
International Collaboration of Trialists, 1999[22]	No	No	Overall: Yes (6/976 total lost to follow) Differential: Yes (4 vs. 2)	Yes	Unclear	Yes	Medium

Appendix F4. Key Question 3: Randomized Controlled Trials Risk of Bias

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
International Collaboration of Trialists, 2011[23]	Unclear. "minimization method for randomly assigning patients was used". Patients stratified by institution, choice of definitive treatment and tumor stage. Each institution selected its preferred definitive local treatment option (cystectomy vs. radiation therapy)	No	Unclear	Yes	NR	NR
Malmstrom, 1996[24]	Unclear	No	Age: Yes Sex: Yes smoking status: NR Bladder cancer stage: No (T1g3 27 vs. 31, T2 52 vs. 64, T3 69 vs. 55, T4 3 vs. 10)	Yes	NR	NR
Millikan, 2001[29] Rintala, 1993[25]	Unclear	No	Yes	Yes	NR	No
Sherif, 2002[26]	Unclear	No	Age: Yes Sex: No (male 116 (75%) vs 133 (86%)) smoking status: NR Bladder cancer stage: Yes	Yes	NR	NR
Skinner, 1991[27]	No: Done to minimize differences between groups, stratified by gender, tumor stage, nodal status and histology	No	Age: Yes Sex: Yes Smoking status: NR Bladder cancer stage: Yes	Yes	NR	NR

Appendix F4. Key Question 3: Randomized Controlled Trials Risk of Bias

Author, Year	Patient Masked?	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to-Treat Analysis?	Postrandomization Exclusions?	Outcomes Prespecified?	Risk of Bias
International Collaboration of Trialists, 2011[23]	No	No Refusal to continue CMV therapy noted at 14/491 but no reports of study withdrawal for either group	Overall: Yes (6/976 total lost to follow) Differential: unclear	Unclear	Unclear	Yes	Medium
Malmstrom, 1996[24]	No	Yes	Overall: Yes (total 2/311) differential: unclear	Yes	No (total 14/325)	Unclear	Medium
Millikan, 2001[29] Rintala, 1993[25]	No	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
Sherif, 2002[26]	No	No	Unclear Unclear	Yes, for survival No, for tumor downstaging	No (total 8/317)	Unclear	Medium
Skinner, 1991[27]	No	No	Unclear Unclear	Unclear	Unclear	Yes	Medium

CMV = cisplatin, methotrexate, vinblastine; G3 = Grade 3; ITT = Intention-to-treat; NR = Not reported; pT2 = Tumor stage 2 determined by pathology; T1 = Tumor stage 1; T2 = Tumor stage 2; T3 = Tumor stage 3; T4 = Tumor stage 4

Appendix F5. Key Question 3: Cohort Studies Risk of Bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Dash, 2008[19]	Yes	Yes	Yes	Unclear	NR	No	No	Unclear	Yes	High
Pal, 2012[30]	Unclear	Yes	Unclear	Yes	NR	No	Unclear	Unclear	Yes	Medium
Wosnitzer, 2012[28]	Yes	No	Unclear	Yes	NR	No	Yes	Unclear	Yes	Medium
Yeshchina, 2012[31]	Yes	Yes	Unclear	Unclear	NR	No	Yes	Unclear	Yes	Medium

NR = not reported

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
1. For patients with non-metastatic muscle-invasive bladder cancer, what is the effectiveness of bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy, and/or maximal transurethral resection of bladder tumor) for decreasing mortality or improving other outcomes (e.g., recurrence, metastasis, quality of life, functional status) compared with cystectomy alone or cystectomy in combination with chemotherapy?							
Bladder preserving external beam radiation therapy (60 Gray) versus radical cystectomy plus radiation therapy (40 Gray): Median survival duration, local recurrence, regional recurrence	1 RCT	High	Cannot determine	Direct	Imprecise	Undetected	Low
Bladder-preserving therapies versus radical cystectomy: Overall survival, bladder-specific mortality, local recurrence, regional recurrence	3 cohort studies	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Bladder-sparing therapy versus radical cystectomy: Quality of life	No studies	-	-	-	-		Insufficient
1a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?							
Bladder-sparing therapy versus radical cystectomy: Effectiveness	No studies	-	-	-	-	-	Insufficient
1b. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?							
Bladder-sparing therapy versus radical cystectomy: Effectiveness	No studies	-	-	-	-	-	Insufficient
1c . What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy?							
Different combinations of chemotherapeutic agents and/or radiation treatment: Effectiveness	No studies	-	-	-	-	-	Insufficient
1d. What is the effectiveness of different bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy and/or maximal transurethral resection of bladder tumor) compared with one another?							
One type of bladder-preserving treatment versus another: Effectiveness	1 cohort study	High	Cannot determine	Direct	Imprecise	Undetected	Insufficient

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
2. For patients with clinically non-metastatic muscle-invasive bladder cancer that is treated with cystectomy, does regional lymph node dissection improve outcomes compared with cystectomy alone?							
Regional lymph node dissection of at least four nodes: Mortality	1 cohort study	Moderate	Cannot determine	Direct	Precise	Undetected	Low
2a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?							
Radical cystectomy with versus without regional lymph node dissection: effectiveness	No studies	-	-	-	-	-	Insufficient
2b. Does the comparative effectiveness differ according to the extent of the regional lymph node dissection (e.g., as measured by the number of lymph nodes removed)?							
More extensive lymph node dissection versus less extensive or standard lymph node dissection: All-cause mortality, bladder cancer-specific mortality	7 cohort studies	Moderate	Inconsistent	Direct	Precise	Undetected	Low
Extent of lymph node dissection: Bladder cancer recurrence or progression	4 cohort studies	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient
3. For patients with non-metastatic muscle-invasive bladder cancer that is treated with cystectomy, does neoadjuvant or adjuvant chemotherapy improve outcomes compared with cystectomy alone?							
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Mortality	4 RCTs	Moderate	Consistent	Direct	Precise	Undetected	Moderate
Neoadjuvant CMV vs. no neoadjuvant chemotherapy: Likelihood of metastasis, likelihood of death	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Undetected	low
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Locoregional bladder cancer recurrence	3 RCTs	Moderate	Consistent	Direct	Precise	Undetected	moderate
Adjuvant chemotherapy vs. no adjuvant chemotherapy: Mortality	4 RCTs	Moderate	Inconsistent	Direct	Precise	Undetected	Low
Adjuvant chemotherapy vs. no adjuvant chemotherapy: bladder cancer progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
Adjuvant chemotherapy vs. no adjuvant chemotherapy: locoregional recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Undetected	Insufficient

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
3a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?							
Adjuvant MVAC versus cisplatin and gemcitabine: comparative effectiveness	2 cohort studies	High	Consistent	Direct	Imprecise	Undetected	Insufficient
3b. Does the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?							
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Effectiveness	3 RCTs	Moderate	Consistent	Direct	Imprecise	Undetected	Low
Adjuvant chemotherapy vs. no adjuvant chemotherapy: Effectiveness	2 RCTs	Moderate	Consistent	Direct	Imprecise	Undetected	Low
3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?							
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy in subgroups based on patient age: effectiveness	3 RCTs	Moderate	Consistent	Direct	Imprecise	Undetected	Low
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy in subgroups of sex, performance status, renal function: effectiveness	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
3d. Does the comparative effectiveness of neoadjuvant or adjuvant chemotherapy differ according to dosing frequency and/or the timing of its administration relative to cystectomy?							
Adjuvant vs. neoadjuvant MVAC: Overall survival, bladder-cancer specific survival	1 RCT 2 cohort studies	Moderate	Consistent	Direct	Imprecise	Undetected	Low
Adjuvant cisplatin plus gemcitabine on day 2 versus day 15: 5-year survival	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
4. What are the comparative adverse effects of treatments for non-metastatic muscle-invasive bladder cancer?							
Bladder-sparing therapies versus radical cystectomy: Adverse events	4 cohort studies	High	Cannot determine (harms reported inconsistently)	Direct	Imprecise	Undetected	Insufficient
Extended lymph node dissection vs. standard lymph node dissection: Operative time	1 cohort study	High	Cannot determine	Direct	Imprecise	Undetected	Low
Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Surgical complications, perioperative deaths	3 RCTs	Moderate	Consistent	Direct	Precise	Undetected	Moderate
Neoadjuvant chemotherapy: Grade 3 or 4 hematological adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Undetected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Adjuvant chemotherapy vs. No adjuvant chemotherapy: adverse events	3 RCTs	High	Consistent	Direct	Imprecise	Undetected	Insufficient
Neoadjuvant vs. adjuvant MVAC: Mortality related to chemotherapy toxicity	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low

CMV = cisplatin, methotrexate, vinblastine; MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; RCT = randomized controlled trial; SOE = strength of evidence

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